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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/022,073	12/13/2001	Yiyou Chen	GC713	5600

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H. Thomas Anderton Jr., Esq.
Genencor International, Inc.
925 Page Mill Road
Palo Alto, CA 94304

EXAMINER
SWOPE, SHERIDAN

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 04/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/022,073	CHEN ET AL.	
	Examiner	Art Unit	
	Sheridan L. Swope	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 February 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *19-21 and 35-37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18 and 22-34* is/are rejected.

7)☒ Claim(s) *22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of Invention I, Claims 1-18 and 22-34 in Paper No. 13 is acknowledged. Claims 19-21 and 35-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected Inventions, there being no allowable generic or linking claim. Claims 1-18 and 22-34 are hereby considered on their merits.

Specification-Objections

The specification is objected to for citing priority in the first paragraph to a provisional application by the Attorney Docket number, GC684-20. The citation should be corrected to the provisional application number, as cited in the Declaration.

The font for the temperature symbol (°) is incorrect; see page 79, paragraph 5 and elsewhere. Correction is required.

On page 94, line 24, there is an incomplete parenthesis ie "...quantities of targeted β-lactamase BLA) molecules". Correction is required.

Claims-Objections

Claim 22 is objected to under 37 CFR 1.75(c), for being confusing. Claim 22 recites a composition comprising the targeted enzyme of Claim 1 and a pharmaceutically acceptable carrier, excipient, or diluent and, as such, recites the same composition as Claim 1, from which it dependents. Applicant is required to cancel the claim, or amend the claim to place the claim in proper dependent form, or rewrite the claim in independent form.

Claim Rejections - 35 USC § 112-Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-11, 14-18, and 22-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "variant sequences" renders these claims indefinite. For example, Claim 5 is unclear in reciting "...one of the targeting sites comprises two variant sequences". Does this mean that there are two amino acid residues in the targeting site that are different from the pretargeted protein? Or alternatively, does it mean that the targeting site has two motifs, comprised of stretches of amino acid residues, or that it can be two polypeptides that are different from the pretargeted protein? The size of a "variant sequence" has not been defined. Claims 1-4, 6-11, 14-18, and 22-34 are rejected for the same reasons. Clarification is required. Note for purposes of examination, it was assumed that the variant sequence can be any size.

Claims 1-18 and 22-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. It is unclear if the targeting site can be one or any of: (i) mutation of specific residues in the pretargeted enzyme, (ii) insertion of a stretch of amino acids comprising around 25 residues into the pretargeted enzyme, or (iii) addition of more than 25 residues to the pretargeted enzyme resulting in the formation of a fusion protein. Clarification is required. Note for purposes of examination, it was assumed that the targeting sequence can be any of (i), (ii), or (iii), as described.

Claim 9 is unclear in reciting "...comprises two variant sequences targeted enzyme" and, thus, is rejected under 35 U.S.C. 112, second paragraph. Correction is required.

Claim Rejections - 35 USC § 112-First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-18 and 22-34 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the β-lactamase (pdb accession # 1bls) with a target site for streptavidin in the B-loop, made as described on page 89 line 28-page 91 line 6 and then isolated by p-aminophenylboronic acid affinity chromotagraphy followed by streptavidin chromatography as described on page 95 line 17-page 97 line 12, does not reasonably provide enablement for any targeted enzyme comprised of any enzyme activity or any targeting site, including two or three different sites. The specification is not enabling for a targeted enzyme wherein the targeting site is engineered at any variation-tolerant site in the pretargeted enzyme. Furthermore, the specification is not enabling for a targeted enzyme wherein the targeting site has two or more variant sequences. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1-16 and 22 are so broad as to encompass any targeted enzyme comprising any enzyme activity while, Claim 17 is so broad as to encompass any targeted enzyme comprising any activity of a protease, carboxypeptidase, β-lactamase, asparaginase, oxidase, hydrolase, lyase, lipase, cellulase, amylase, kinase, phosphatase, transferase, aldolase, or reductase. Claims 1-18 and 22-34 are so broad as to encompass a targeted enzyme comprising any targeting site including two or three different sites. Claims 5-8, 17, 22, 27-30, and 32, are so broad as to

encompass any targeted enzyme comprising a targeting site wherein the targeting site comprises two or three variant sequences. Claims 1-18 and 22-33 are so broad as to encompass any targeted enzyme wherein the targeting site is engineered at any variation-tolerant site in the pretargeted enzyme. The scope of each of these claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of targeted enzymes broadly encompassed by the claim. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired targeted enzyme activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. However, in this case the disclosure is limited to a β-lactamase with a target site for streptavidin.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the results of such modifications are unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of Claims 1-16 and 22 which, encompasses any targeted enzyme comprising any enzyme activity or Claim 17 which encompasses any targeted enzyme comprising any activity of a protease, carboxypeptidase, β-

lactamase, asparaginase, oxidase, hydrolase, lyase, lipase, cellulase, amylase, kinase, phosphatase, transferase, aldolase, or reductase. The specification does not support the broad scope of Claims 1-18 and 22-34 which encompass a targeted enzyme comprising any targeting site including two or three different targeting sites. The specification does not support the broad scope of Claims 5-8, 17, 22, 27-30, and 32, which encompass any targeted enzyme comprising a targeting site wherein the targeting site comprises two or more variant sequences. The specification does not support the broad scope of Claims 1-18 and 22-33 which encompass any targeted enzyme wherein the targeting site is engineered at any variation-tolerant site in any pretargeted enzyme.

The specification does not support the broad scope of Claims 1-17 and 22 because the specification does not establish: (A) all pretargeted enzymes that can be modified to make an active targeted enzyme; (B) the general tolerance of the enzymatic activity of any pretargeted enzyme to modification as a targeted enzyme and extent of such tolerance; (C) a rational and predictable scheme for modifying any enzyme into a targeted enzyme with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of enzymes is likely to be successful as a targeted enzyme.

The specification does not support the broad scope of Claims 1-18 and 22-34 because the specification does not establish: (A) which targeting sites, including two or three different sites, that can be used to convert any pretargeted enzyme into an active targeted enzyme; (B) the general tolerance of any enzyme activity to incorporation of any targeting site, including two or three different sites; and extent of such tolerance; (C) a rational and predictable scheme for

incorporating any specific targeting site, including two or three different sites, into any enzyme with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of targeting sites is likely to be successful for any enzyme.

The specification does not support the broad scope of Claims 5-8, 17, 22, 27-30, and 32, because the specification does not establish: (A) all regions of any targeting site that may be modified without effecting the targeting activity; (B) the general tolerance of the activity of any targeting site to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any targeting site with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of modified targeting sites is likely to be successful.

The specification does not support the broad scope of Claims 1-18 and 22-33 because the specification does not establish: (A) regions of any pretargeted enzyme structure which are variation tolerant; (B) the general tolerance of the enzymatic activity of any pretargeted enzyme to modification at any variation-tolerent site and extent of such tolerance; (C) a rational and predictable scheme for modifying any variation-tolerant site with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices of variation-tolerant sites, and modification thereof, are likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a large number of targeted enzymes consisting of an enormous

number of amino acid modifications of any pretargeted enzyme. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the identity of sequences having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 1-18 and 22-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to a genus of targeted enzymes comprised of any enzyme activity or any targeting site, including two or three different sites. The specification teaches how to make only a single representative species of such targeted enzyme and does not teach the structure of said representative species. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of being a targeted enzyme. Given this lack of description of representative species encompassed by the genus of the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 12, 14, 16, 17, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakanishi et al, 1997. Nakanishi et al teach a targeted carbonyl reductase enzyme wherein there is a $T^{38}D$ substitution in the reductase. Said substitution does not affect the catalytic activity of the reductase but converts the coenzyme specificity from NADP(H) to NAD(H) with an approximately 1,300-fold change in specificity (page 2219, parg 11). Thus, Nakanishi et al teach a targeted enzyme wherein a site is altered by a one amino acid residue variation so that the targeting site binds coenzyme NAD(H) while, the pretargeted enzyme does not bind NAD(H). The molecular weight of the targeted reductase is less than 45kDa (Fig 1). Therefore, Claims 1, 12, 14, 16, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakanishi et al, 1997.

Claims 1-3, 5-7, 9-17, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Maier et al, 1999. Maier et al teach a targeted reverse transcriptase wherein, said transcriptase is tagged at the N-terminus with glutathione reductase (GST) and at the C-terminus with a 6X-His-tag (pg 11, parg 7). The targeted transcriptase was fully active (Fig 1B, clone 3). Said targeted reductase binds glutathione and nickel while, the pretargeted enzyme does not. Therefore, Claims 1-3, 5-7, 9-17, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Maier et al, 1999.

Claims 1, 15, 16, 17, 18, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Vrudhula et al, 1993 or Meyer et al, 1992. Vrudhula et al teach an enzymatically active conjugate wherein β-lactamase is fused to a monoclonal antibody directed to antigens present on

tumor cell surfaces (Fig 4). Meyer et al teach an enzymatically active conjugate wherein β-lactamase is fused to a FAB fragment directed to carcinoembryonic antigen (Table I). Therefore, Claims 1, 15, 16, 17, 18, and 22 are rejected under 35 U.S.C. 102(b) as being anticipated by Vrudhula et al, 1993 or Meyer et al, 1992.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 23-25, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verdet et al, 1999 in view of Maier et al, 1999, Vrudhula et al, 1993 or Meyer et al, 1992 and further in view of Barthelemy et al, 1992. Verdet et al teach a β-lactamase comprising a KTXS sequence at its substrate recognition site and further comprising a VHKTGSTG sequence (see EMBL Acc#Y15129). Verdet et al do not teach their β-lactamase as a targeted enzyme. The teachings of Maier et al, Vrudhula et al, and Meyer et al are described above. It would have been obvious to a person of ordinary skill in the art to use the methods of Maier et al, Vrudhula et al, or Meyer et al to prepare a targeted enzyme from the β-lactamase of Verdet et al. The preparation of targeted β-lactamases is suggested by Vrudhula et al, wherein, they state that β-lactamase meets the criteria necessary for use as a targeted enzyme (pg 334, parg 2). Motivation to use the methods of Maier et al, Vrudhula et al, or Meyer et al to prepare a targeted enzyme from the β-lactamase of Verdet et al derive from the advantage of using targeted β-lactamases as anti-tumor pharmaceuticals (Vrudhula et al and Meyer et al). Motivation is further provided by

the fact that the β-lactamase of Verdet et al has a serine at position 237 in the substrate binding site which, as taught by Barthelemy et al, extends the substrate specificity (page 21, lines 8-11). The expectation of success is high as, preparation of targeted enzymes is known in the art. Therefore, Claims 23, 24, 25, 31, and 33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Verdet et al, 1999 in view of Maier et al, 1999, Vrudhula et al, 1993 or Meyer et al, 1992 and further in view of Barthelemy et al, 1992.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sheridan L. Swope whose telephone number is 703-305-1696. The examiner can normally be reached on M-F; 9:30-7 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Sheridan L. Swope, Ph.D.

REBECCA E. PRUTY
PRIMARY EXAMINER
GROUP ~~1600~~ 1640